PCT

WELTORGANISATION FÜR GEISTIGES EIGENTUM
Internationales Büro

INTERNATIONALE [redacted]ELDUNG VERÖFFENTLICHT NACH DE[redacted]ERTRAG ÜBER DIE INTERNATIONALE ZUSAMMENARBEIT AUF DEM GEBIET DES [redacted]ENTWESENS (PCT)

(51) Internationale Patentklassifikation 5 : C09K 3/30, A61K 9/72

A1

(11) Internationale Veröffentlichungsnummer: WO 91/11496

(43) Internationales Veröffentlichungsdatum: 8. August 1991 (08.08.91)

(21) Internationales Aktenzeichen: PCT/EP91/00178

(22) Internationales Anmeldedatum: 31. Januar 1991 (31.01.91)

(30) Prioritätsdaten:
P 40 03 270.1 3. Februar 1990 (03.02.90) DE

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(81) Bestimmungsstaaten: AT (europäisches Patent), AU, BE (europäisches Patent), CA, CH (europäisches Patent), DE (europäisches Patent), DK (europäisches Patent), ES (europäisches Patent), FI, FR (europäisches Patent), GB (europäisches Patent), GR (europäisches Patent), HU, IT (europäisches Patent), JP, KR, LU (europäisches Patent), NL (europäisches Patent), NO, PL, SE (europäisches Patent), SU, US.

Veröffentlicht
Mit internationalem Recherchenbericht.
Vor Ablauf der für Änderungen der Ansprüche zugelassenen Frist. Veröffentlichung wird wiederholt falls Änderungen eintreffen.

(54) Title: NOVEL VEHICLE GASES AND THEIR USE IN MEDICAL PREPARATIONS

(54) Bezeichnung: NEUE TREIBGASE UND IHRE VERWENDUNG IN ARZNEIMITTELZUBEREITUNGEN

(57) Abstract

Besides 1,1,1,2,3,3,3-heptafluoropropane, novel advantageous vehicle gases may contain one or more further vehicle gas components and may be used in medical preparations.

(57) Zusammenfassung

Neue vorteilhafte Treibgase enthalten neben 1,1,1,2,3,3,3-Heptafluorpropan gegebenenfalls eine oder mehrere weitere Treibgaskomponenten und können in Arzneimittelzubereitungen Verwendung finden.

New propellants and their use in pharmaceutical preparations

The invention concerns

- new propellants in which 1.1.1.2.3.3.3-heptafluoropropane (TG 227) is contained as the typical component;
- the use of these propellants in pharmaceutical preparations that are suitable for the production of aerosols; and
- the pharmaceutical preparations themselves.

Aerosols of powdery (micronized) medicinal agents are frequently used in therapy--for instance, in the therapy of obstructive respiratory diseases.

To the extent that these aerosols are not produced by atomizing the medicinal powder, or by spraying solutions, suspensions of the medicinal agents in liquified propellants are used.

For that purpose, use is made mainly of mixtures of TG (11 (trichlorofluoromethane), TG 12 (dichlorodifluoromethane), and TG 114 (1.2.-dichlorine-1.1.2.2-tetrafluoroethane), possibly with the addition of low alkanes--for instance, butane, pentane, or DME (dimethylether). Mixtures of this kind are known, for instance, from German patent application 1 178 975.

The use of chlorofluorocarbons has become a problem because of their negative influence on the earth's atmosphere (destruction of the ozone layer, greenhouse effect), with the result that the search was on for other propellants or propellant mixtures that do not have the mentioned negative effects, or at least to a lesser degree.

However, the search encounters considerable difficulties because propellants that are to be used therapeutically, have to meet numerous criteria that are difficult to bring into harmony--for instance, with respect to toxicity, stability, vapor pressure, density, and dissolution behavior.

As was discovered, TG 227 (1.1.1.2.3.3.3-heptafluoropropane), possibly in a mixture with one or more propellants from the group TG 11 (trichlorofluoromethane), TG 12 (dichlorodifluoromethane), TG 114 (1.2-dichlorine-1.1.2.2-tetrafluoroethane) propane, butane, pentane, and DME are especially suitable for use in therapeutically applicable preparations.

The components applicable in addition to TG 227 are added if the properties of the propellant are to be modified--for instance, if another density of the liquified propellant, another pressure, or another dissolution behavior is to be established.

Pharmaceutical preparations on the basis of the new propellant contain an active ingredient in a finely distributed form, generally as a suspension, and further, generally, surface-active materials--for instance, a phospholipid such as lecithin, an ester of a polyalcohol (such as sorbitol) with higher saturated and unsaturated fatty acids (e.g., stearic, palmitic, and oily acids), for instance sorbitan trioleate, or a polyethoxysorbitan ester of a higher, preferably unsaturated fatty acid.

The suspensions produced with the new propellant tend to separate, in part. However, it has become evident that those separated suspensions can easily be distributed evenly in the suspension medium, by shaking.

The quantity ratios of the individual mixture components of the propellant can vary within broad boundaries. The proportion (expressed, in each case, in a percentage by weight) is 10-100% for TG 227.

In addition, the mixture can contain up to 50% of propane and/or butane and/or pentane and/or DME and/or TG 11 and/or TG 114. Within the mentioned boundaries, the components are chosen in such a way that the total amounts to 100%. Propellant mixtures that contain 30-100% of TG 227 are preferred.

The proportion of suspended medicinal agent in the finished preparation is between 0.001 and 5 %, preferably 0.005 to 3%, and especially 0.01 to 2%.

The surface-active materials are added in quantities of 0.01 to 10%, preferably 0.05 to 5%, and especially 0.1 to 3%. (As with the medicinal agents, the percentage by weight of the finished preparation is indicated.)

All substances suitable for inhalational, possibly also for intranasal, application can serve as medicinal agents in the new preparations.

Accordingly, the following are especially concerned: betamimetic agents, anti-cholinergic agents, steroids, antiallergic agents, PAF antagonists, and combinations of these active ingredients. Specifically, the following should be mentioned as examples.

<u>As betamimetic agents:</u>

bambuterol
bitolterol
carbuterol
clenbuterol
fenoterol
hexoprenalin
ibuterol
pirbuterol
procaterol
reproterol
salbutamol
salmeterol
sulfonterol
terbutalin
tulobuterol

1-(2-fluorine-4-hydroxyphenyl)-2-[-4-(1-benzimidazolyl)-2-methyl-2-butylamino] ethanol;

erythro-5'-hydroxy-8'-(1-hydroxy-2-isopropylaminobutyl)-2H-1.4-benzoxazin-3-(4H)-on;

1-(4-amino-3-chlorine-5-trifluoromethylphenyl)-2-tert.butyl-amino) ethanol; and

1-(4-ethoxycarbonylamino-3-cyanogen-5-fluorophenyl)-2-(tert.-butylamino) ethanol.

As anticholinergic agents:

iprotropiumbromide
oxitropiumbromide
trospiumchloride
benzilic acid-N-ß-fluoroethyl nortropinester methobromide

As steroids:

budesonide
beclometasone (or 17.21-diproprionate)
dexamethasone-21-isonicotinate
flunisolide

As antiallergic agents:

disodiumcromoglicate
nedocromile

As PAF antagonists:

WEB 2086
WEB 2170
WEB 2347

The active ingredients can also be combined--for instance, betamimetic plus anticholinergic agents, or betamimetic plus antiallergic agents.

Examples of preparations according to the invention (indicated in percentage by weight):

1.		2.	
0.10%	of oxitropiumbromide	0.3%	of fenoterol
0.01%	of soybean lecithin	0.1%	of soybean lecithin
4.0%	of pentane	10.0%	of pentane
95.89%	of TG 227	70.0%	of TG 227
		19.6%	of TG 12[illegible]

3. 0.1% of iprotropiumbromide
0.1% of soybean lecithin
20.0% of propane
20.0 of butane
49.8% of TG 11

4. 0.3% of fenoterol
0.1% of soybean lecithin
30.0% of TG 11
69.6% of TG 227

5. 1.5% of disodiumcromoglicate
0.1% of tween 20
98.4% of TG 227
1.4% of butane

6. 0.3% of salbutamol
0.2% of span 85
20.0% of pentane
60.0% of TG 227
19.5% of TG 12

7. 0.15% of fenoterol
0.06% of iprotropiumbromide
0.10% of soybean lecithin
40.00% of TG 11
19,69% of propane
40.00% of TG 227

8. 0.1% of iprotropiumbromide
0.1% of soybean lecithin
15.3% of propane
30.5% of TG 11
54.0% of TG 227

Patent claims

1. Propellants characterized by a content of TG 227, possibly in a mixture with one or more propellants from the group TG 11, TG 12, TG 114, propane, butane, pentane, and DME.

2. Propellants according to claim 1, with the characteristic that they contain, in addition, at least one surface-active substance.

3. Propellants according to claim 2, with the characteristic that the surface-active substance is a phospholipid, a sorbitan ester with a higher saturated or unsaturated fatty acid, or a polyethoxysorbitan ester of a higher, preferably unsaturated fatty acid.

4. Propellants according to claim 2, with the characteristic that the surface-active material is a lecithin, a polyoxyethylene-sorbitan oleate, or a sorbitan trioleate.

5. Pharmaceutical preparations for the production of powder aerosols on the basis of propellant mixtures according to claims 1, 2, 3, or 4, with the characteristic that they contain, as active ingredients, a betamimetic agent, an anti-cholinergic agent, a steroid, an antiallergic agent, a PAF antagonist, or a combination of these compounds.

6. Pharmaceutical preparations according to claim 5, with the characteristic that the following are used:

as betamimetic agents:

bambuterol
bitolterol
carbuterol
clenbuterol
fenoterol
hexoprenalin
ibuterol
pirbuterol
procaterol
reproterol
salbutamol
salmeterol
sulfonterol
terbutalin
tulobuterol

1-(2-fluorine-4-hydroxyphenyl)-2-[-4-(1-benzimidazolyl)-2-methyl-2-butylamino] ethanol;

erythro-5'-hydroxy-8'-(1-hydroxy-2-isopropylaminobutyl)-2H-1.4-benzoxazin-3-(4H)-on;

1-(4-amino-3-chlorine-5-trifluoromethylphenyl)-2-tert.butyl-amino) ethanol; and

1-(4-ethoxycarbonylamino-3-cyanogen-5-fluorophenyl)-2-(tert.-butylamino) ethanol.

as anticholinergic agents:

iprotropiumbromide
oxitropiumbromide
trospiumchloride
benzilic acid-N-ß-fluoroethyl nortropinester methobromide

as steroids:

budesonide
beclometasone (or 17.21-diproprionate)
dexamethasone-21-isonicotinate
flunisolide

as antiallergic agents:

disodiumcromoglicate
nedocromile

as PAF antagonists:

WEB 2086
WEB 2170
WEB 2347

7. Pharmaceutical preparations according to claim 5, with the characteristic that the combination of active ingredients includes one of the betamimetic agents mentioned in claim 6 and one of the anticholinergic agents mentioned in claim 6.

8. Pharmaceutical preparation according to claim 5, with the characteristic that the combination of active ingredients includes one of the betamimetic agents mentioned in claim 6 and disodiumcromoglicate.

9. Pharmaceutical preparation according to claim 5, with the characteristic that the combination of active ingredients contains one of the betamimetic agents mentioned in claim 6 and one of the PAF antagonists mentioned in claim 6.

10. Pharmaceutical preparation according to claim 5, with the characteristic that the combination of active ingredients includes disodiumcromoglicate and one PAF antagonist mentioned in claim 6.

11. Method for the production of pharmaceutical preparations according to claims 5-10, with the characteristic that active medicinal agents, micronized according to customary methods, are suspended in a liquified propellant mixture according to claim 1, 2, 3, or 4.

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738-7605